

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6962

Title: Gender-related differences in IBS: Potential mechanisms of sex hormones

Reviewer code: 02531171

Science editor: Qi, Yuan

Date sent for review: 2013-10-31 16:22

Date reviewed: 2013-11-18 18:09

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

The manuscripts entitled 'Gender-related differences in IBS: Potential mechanisms of sex hormones' by Meleine and Matricon provides a very comprehensive review of the literature on IBS with a focus on the importance of gender and sex hormones in the onset of the disorder. The manuscript is generally well written, however there are numerous typographical and grammatical (problems with the use of 's' for pluralism and possession) which would benefit a review by a native English speaker. The major comment is that the review would benefit from being more concise and focussed. In a special edition journal it's likely that the general description of factors contributing to IBS will be described by others, this manuscript should focus on the effects of gender and sex hormones on IBS. Thus, a couple of introductory sentences, rather than two paragraphs should be sufficient prior to discussing the influence of sex hormones on IBS. This will also reduce the number of references which are abundant (>300). Clearly describe the changes in hormones during the menstrual cycle so that the reader can make conclusions regarding the changes in IBS symptoms at different stages during the cycle. Also, only list the key points at the end of the manuscript to take all the information as a whole rather than after each section. Include a figure to summarise the proposed integrative model. Minor comments: Please complete lists. Do not end with '.....' or 'etc'. The abstract seems quite long (>400 words). Include running title and key words. Pg 6: dysbiosis of what? Pg 10: surely other factors in pregnancy such as displacement of bowel, changes in diet and reduced activity are also likely to influence GI transit time? Pg 10: it's not clear what is meant by 'fundamental' studies - basic science? Pg 13: male and 'female' IBS patients sounds better than 'male and women IBS.' Pg 23: it's unclear what 'wind-up' of the spinal cord means. Please explain

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6962

Title: Gender-related differences in IBS: Potential mechanisms of sex hormones

Reviewer code: 02721496

Science editor: Qi, Yuan

Date sent for review: 2013-10-31 16:22

Date reviewed: 2013-12-05 21:06

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Major revision

COMMENTS TO AUTHORS

In this review the authors aim to evaluate the role of sex hormones on IBS by describing the possible effect on physiological mechanism meant to contribute to IBS symptomatology. The authors somehow succeed in doing so as the review is very well written and explain some very complex mechanisms. But the review needs major revision before it can be published. See comments below.

Generally:

- The review is way too long!!! 43 pages exceeds standards for reviews published in journals. It is beyond my understanding why the authors have submitted an abstract this long as it is not realistic to have it published in its current length. Furthermore the authors should be aware that this puts a significant workload to the reviewers.
- As a consequence of the previous comment the authors seriously need to prioritize what should be included in the review. This review covers a very large subject with many aspects explained thoroughly. My proposal is to leave the basic physiological explanations out even though they are well written. Focus on the topic- the affect of the sexhormones and how this could lead to IBS symptoms.
- The authors needs to be very aware of not describing the female hormones as disease causing per se, as most women live a life without symptoms of IBS. It could be more clear and underlined more how these hormones could make women more susceptible to developing symptoms of IBS (and why they are not disease causing in most women). Because the abstract

is so long and contains so much information this important point is not as clear as it should be.

- The authors should comment on the fact that in the Rome III questionnaire for IBS, a patient can not be defined as having IBS if symptoms only occur during menstrual bleeding. (<http://www.romecriteria.org/pdfs/IBSMode.pdf>) I know the authors do not state that sex hormones could only cause symptoms during the menstrual bleeding but more than once symptoms are described as worsened during menstrual bleeding. It should be argued from the authors how sex hormones could play a role in the development of IBS symptoms even though the mentioned exclusion criteria exists in the Rome III questionnaire.
- The review should be readable to gastroenterologists. Phrases like "perimenses", "met/diestrus" should be explained first time they are mentioned.
- An illustration of how the sex hormones potentially could lead to IBS symptoms could be very usefull. It could give a quick overview.

Specific comments:

Key words: Some of the key words are to general; e.g. human., symptoms, genes enviromen

Abbreviations: It is standard to abbreviate Constipation predominant IBS: IBS-C and not C-IBS as written in the manuscript. Same goes for IBS-D and A. Not all abbreviations are included (e.g. HPA).

Abstract:

-The method should be described more detailed. See comment on method in general.

-The first line in the conclusion does not make any sense : "Although they do not influence clinical...": As IBS is not an organic disorder per se,the diagnosis relies on the clinical presentation, so if sex hormones do not indfluence clinical presentation of IBS are they then relevant at all? I do not think this sentence represents what is written in the manuscript.

Introduction:

-Reference 1 and 2 could be more updated. There are more recent reviews on the prevalence of IBS.

- It is argued that there is a strong correlation between dysmenorrhea and IBS, and perimenses exacerbation of abdominal pain have been observed. In relation to this the authours need to comment on the exclusion criteria in the Rome III questionnaire as mentioned in the general comments.

Method:

This section needs to be much more detailed, see the PRISMA statement for guidelines on how the method of a systematic review should be described (<http://www.prisma-statement.org/statement.htm>) e.g. there needs to be information on number of papers included/excluded etc.

1. Female gender and influence of ovarian hormones on GI motility:

Page 10

-Reference 35 concludes the opposite of what the authors write. Low low estrogens levels are associated to faster transit time and not reduction in transit time as written. Furthermore this reference concludes it is the upspeed in transit time that lowers the estrogen levels and not the other way around.

-It is stated that GI transit is prolonged during the third trimester of pregnancy as an argument for ovarian hormones playing a role in GI motility. Motility could also simply be prolonged as a consequence of the baby taking up space in the abdomen, making transit more difficult? This observation is not transferable to women with irritable bowel syndrome?

Page 13

The last section just before key points describes ovarian hormones and 5-HT possible impact on GI transit. This is one of the sections referred to in general comments where it needs to be more clear how this is related to disease. These hormones also fluctuate in healthy women.

b. Alterations of central pain processing...

Page 17

In the second sentence it is written "This multimodal treatment..." . What treatment is referred to? It is not clear.

b. Gender differences in central visceral pain...

Page 23

In the last sentence on the page it is written: "Indeed, women display differences..., such as "wind-up" in the spinal cord for instance". What does wind-up mean? This needs to be more clear!

3. stress and female gender in IBS

In the last sentence of the section on page 29 it is hypothesised that that early stress experience can influence autonomic and HPA response even though the opposite was concluded from reference 220 and 235 on page 28?? The hypothesis appears very speculative and not very well argued for.

4. Stress, ovarian hormones...

Page 30

It is written: "These data give further support to the idea that overactivity of CRH signalling in the brain and the gut may explain the comorbidity of stress, depression and IBS in women": Again this seems like speculation as the opposite is concluded from reference 220 and 235 on page 28. Hypothesis should not be made from studies on rodents when studies on IBS patients show the opposite.

Page 31:

IBSI should be corrected to IBS

2. Estrogens and the gut barrier

Page 32

-Reference 285 is referred to as describing colonic epithelium. This is wrong! The reference describes uterine epithelium. It is not relevant to include this reference in the review.

- It is not relevant to mention ERs effect on endothelial and cervical endothelium and breastcancer cells.

Focus on the topic of the review!

4. Ovarian hormones..

Page 34

The last sentence of the section is too long. It is too difficult to understand!

II. proposed integrative...

Page 41

-The first sentence of the section does not make sense. Needs to be corrected.

-It is described that ovarian hormones act as a trigger factor to further sensitize this priming and ultimately contribute to onset of IBS. It does not seem likely as these hormones are a natural part of puberty. The authors